REMARKS

Applicants file a Request for Continued Examination (RCE) herewith.

Claim 1 has been amended and claim 4 has been cancelled without prejudice. No new matter has been added by virtue of the amendments. No new matter has been added by virtue of the amendments. For instance, support for the amendments appears in the original claims of the application.

Applicants request consideration of the Information Disclosure Statement filed July 30, 2004.

Applicants respond as follows to prior Office Action and Advisory Action.

Claims 1-7, 9, 12-14, 21-24, 35, 39-41, 44-46, 51, 54, 76 and 83-85 were rejected under 35 U.S.C. §103(a) as being unpatentable over German Pat. No. 44 47 287 C1 in view of US Patent 5,322,685 (US '685). In the prior Office Action, the Office asserted that:

> Applicant's claims are directed toward a topical composition that is able to penetrate the pores even when the pores are smaller than the diameter of the penetrants. The composition is disclosed by applicant as being described in DE '287 (see page 2, first paragraph or applicant's specification). DE '287 refers to the composition as "transfersomes." The transfersomes in DE '287 can contain the antioxidant BHT (see English translation, page 25, second paragraph). The transfersomes can also contain glucocorticoids and mineral corticoids (see page 24 of English translation).

Applicant respectfully traverses this rejection.

Applicants' independent claim 1 (the only pending independent claim) reads as follows:

Claim 1. A formulation comprising penetrants being capable of penetrating the pores of a barrier, the average diameter of said pores being smaller than the average diameter of said penetrants, wherein said penetrants can transport agents or enable agent penetration through said pores after said penetrants have entered said pores, wherein the formulation further comprises

1) at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per 6 months; and

2) at least one microbiocide in an amount that reduces the bacterial count of 1 million germs added per gram of total mass of the formulation to less than 100 in the case of aerobic bacteria, to less than 10 in the case of entero-bacteria, and to less than 1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days;

wherein the agent is selected from corticosteroids and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation.

The cited documents, whether considered alone or in combination, do not suggest that claimed formulation.

More particularly, among other things, none of the cited documents suggest a formulation as Applicant claims that comprises at least one antioxidant in an amount that reduces the increase of oxidation index to less than 100% per six months.

Moreover, in addition to failure to disclose use of an oxidant, the cited documents also fail to disclose use of at least one microbiocide as recited in Applicants' claim 1.

Indeed, ultradeformable vesicles as disclosed in the present application are unique drug carrier systems, where varying composition changes can impact the resulting carrier ability to cross a semipermeable barrier such as the skin.

As acknowledged in the Office Action, DE '287 does not describe a preparation wherein the agent (active substance) is a corticosteroid and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, as claimed by Applicants.

Further, DE '287 does not suggest a preparation wherein the agent (active substance) is a corticosteroid and the relative content of corticosteroids is above 0.1 weight-%, relative to total dry mass of the formulation, as claimed by Applicants. DE '287 describes preparations that include at least two different amphiphile components having different solubilities (a more soluble component and a less soluble component). In a limited situation, DE '287 sets out that the active substance can be the **more soluble** component. In this limited situation, it is set out that:

> Where the active substance, for example, Ibuprofin, Diclofenac or a salt thereof is the more soluble component, possibly with the addition of less than 10% by weight related to the total composition of the preparation of another soluble component and wherein the concentration of the more soluble component(s) typically amounts to between 0.01% by weight and 15% by weight. (English translation, page 25, lines 4-9)

Thus, according to DE '287, if, and only if, the active agent is the more soluble component, then it can be present in an amount between 0.01% by weight and 15% by weight. However, as previously discussed by Applicant, in no event would the more soluble component be a corticosteroid. Rather, this limited situation applies to certain active substances. In particular, as set out by DE '287, the solubility of the components refers to their solubility in the suspension medium, which is usually water (page 10, lines 5-7). It is well-known that corticosteroids are relatively extended, apolar molecules, which are **not at all soluble** or are, at best, **very poorly soluble** in water (the suspension medium). In no event would a corticosteroid be the more soluble component. As such, the limited situation and the parameters associated with this limited situation would not apply to corticosteroids.

In particular, DE '287 only describes that agents (1) that are soluble in the liquid medium (water) and (2) that are more soluble in the liquid medium (water) than the other ampophilic

component can be present in an amount between 0.01% by weight and 15% by weight. This range does not generally relate to active agents, but only to active agents acting as the more soluble component. Corticosteroids will never be the more soluble component and, thus, this range would not apply to corticosteroids. Further, there is no teaching or suggestion that the ranges specified for the more soluble component could apply to anything other than the more soluble component (in this case, a corticosteroid, which would be the less soluble component).

Further, Applicants respectfully disagree with the Office's assertion that even though "The reference (DE '287) does not specifically discuss a formulation that contains the corticosteroids":

> * * *the reference does teach that the amounts of the active ingredients and the carrier substances can be varied to produce a product with the optimum solubility and skin penetration characteristics. Therefore, the reference clearly teaches that the amount of the corticosteroids in the transfersome can be varied in the course of producing the best product possible. Thus, a person of ordinary skill in the art would be motivated to modify the amount of corticosteroid in the transfersome. Such modification would reasonable lead to the amount of corticosteroid claimed by applicant.

The selection of the suitable amount of agents in a preparation involves a number of factors that must be taken into account. While a particular amount may provide efficiency in delivery, undesirable side effects may be associated with such amounts and, thus, a balance must be reached between providing efficient delivery of an effective dose, while, at the same time, minimizing undesirable side effects. This is not a trivial problem, as is demonstrated by the vast number of formulations on the market for delivery of the same agents. These formulations vary significantly in their composition and, thus, it is demonstrated that "producing the best product possible" will not result in the same end product, or even similar end products with similar components and/or concentrations, due to the large number of possible components and variables which can be taken into account and modified. This lack of a single way of "producing the best product possible" is also demonstrated by the continuing need, to date, for providing improved formulations with better delivery with minimal undesirable side effects.

In particular, in formulating a preparation for the delivery of an agent, it is important to deliver a therapeutically effective amount of agent. However, when delivery is through the pores of the skin, for example, the amount of agent in the preparation that is applied to the skin is not necessarily the amount that is ultimately be delivered through the skin to the delivery site. Thus, the selection of the amount of an agent in a preparation is not a straight-forward task. Administration of corticosteroids in amounts between a few micrograms per square centimeter (for most potent corticosteroid agents) and up to a milligram per square centimeter (for less potent corticosteroid agents) is common. Application below these amounts reduces the ability of the agent to permeate into the skin in a therapeutically acceptable level. Application above these amounts can result in intolerable local, or even systemic, side effects. In particular, raising the concentration of the agent incurs the danger of agent precipitation on the skin and increases the likelihood of side effects. For example, skin irritation is a serious obstacle for successful development and application of a preparation. Still further, the complexity in selecting a suitable amount of agent is further increased because one must determine whether more systemic or more topical drug action is to be achieved. As set forth above, the required dose of a corticosteroid depends on which specific corticosteroid is being administered. Further, the potential side effects varies for different corticosteroids. For example, more gentle acting agents, like hydrocortisone, only exhibit a rather short and weak activity. The more recently developed agents, such as prednicarbat- or triamcinolone-derivatives, are more potent, act longer, and are more harmful to the body as they can evoke severe side effects if they are applied highly concentrated and/or repeatedly. Therefore, the selection of dosage must be very precise and depends on which type of agent, and further, which particular agent within that group of agents (e.g. which specific corticosteroid) will be used.

The complexity in choosing an agent and concentration is further demonstrated by the enclosed review article by B. Reazzini and N. Pimpinelli, *New and Established Topical Corticosteroids in Dermatology, Clinical Pharmacology and Therapeutic Use,* Am J Clin Dermatol, 2002 (pp. 47-58). In the past, many structural modifications of the respective agents

have been made in order to improve the efficacy of topical corticosteroids and to produce drugs with greater potency, which, however, has been associated with an increased likelihood of side effects. For example, betamethasone dipropionate and clobetasol propionate, which are typical examples of potent molecules that can control specific dermatoses very rapidly are, however, associated with a high risk of topical and systemic adverse effects. Thus, the administration of corticosteroids is always connected with undesirable side effects, which are directly related to the efficacy of these drugs. It is clearly described that the modification of corticosteroids for achieving greater potency is often associated with a greater potential for adverse effects (p. 48, par 3). The adverse effects caused by corticosteroids are described (page 51) and are mainly sytemic and topical adverse effects. Topically administered corticosteroids are mostly capable of causing local adverse effects (Table III) such as epidermal atrophy, steroid face, and a number of further partially severe local adverse effects. Dermal changes are characterized by dermal thinning, atrophy and loss of collagen bridges and can be even observed after a few months of local therapy because of collagen's long life. It is further mentioned that the changes that occur in collagen fibers are also responsible for the widening of blood vessles, etc.

The atrophogenicity of corticosteroids is known to be generally related to their potency. Therefore, attempts to reduce skin atrophy have been made, for example, the combination of topical corticosteroids therapy with a compound such as an anabolic steroid that will stimulate protein synthesis. However, it is further mentioned that, nevertheless, skin atrophy does not regress after discontinuation of corticosteroids.

Again, on page 53, where clinical formulations are described, it is mentioned that the greater the potency, and the greater the therapeutic efficacy, the greater also are the side effects. Further, it is stated that, when a physician chooses a topical corticosteroid for a specific patient, low potency formulations should be used for long term maintenance therapy. The more potent corticosteroids should be used for short periods and at sites such as palms and soled where low potency corticosteroids are ineffective.

Among the presently used compositions mentioned are ointments, creams, lotions, gels and liposomes. It is stated, however, that liposomes are only valuable delivery systems for topical corticosteroids, where a comprised epidermal barrier enables liposomes to penetrate the skin, which clearly shows that the penetration properties of liposimal delivery systems are not at all optimum.

It is further mentioned with respect to the therapeutic use of topical corticosteroids that the adverse side effects can only be controlled by the use of mild, moderately, or highly potent formulations and depends on where the formulation is to be applied, i.e. dependency on the resistance of the respective skin types. Even a weekly pulsed application of topical potent formulation is described in order to reduce the adverse effects induced by the daily application of very potent topical corticosteroids. (p. 55, 2nd par)

Thus, the review article clearly shown that there are severe problems with side effects of corticosteroids. This article suggests several possibilities to optimize the risk/benefit ratio including: modification of the structure of the active agents, the addition of further ingredients reducing the adverse effects caused by corticosteroids, use of different kinds of formulations which only differ by the use of more or less potent (and, therefore, more or less disadvantageous) agents. It is even suggested that some of the formulations mentioned, namely liposomal formulations, be applied to compromised epidermal barriers as their penetration capability is poor.

Consequently, this article clearly demonstrates that the problems related to the side effects of corticosteroids cannot be solved in a satisfactory manner by present formulations. Therefore, present formulations must be adapted with respect to the potency of the corticosteroid or its amount. Almost all presently approved medicaments containing corticosteroid have corticosteroid contents less than 0.1 weight%. This is because of the adverse effects of

corticosteroids, and is exemplified by the attached list of all medicaments containing clobetasol propionate (a potent corticosteroid) presently approved by the FDA. None of these drugs (be it ointment, cream, solution, gel, etc.) contains more than 0.05% of active agent (corticosteroid). The same also applies to other corticosteroid containing drugs which are presently available.

This clearly establishes that one of skill in the art would not be motivated to raise the amount of corticosteroid in a transfersome formulation because this would cause severe side effects in all of the known formulation types.

The fact that presently available commercial corticosteroid-based products normally contain the active ingredient in a low percentage range is also due to the fact that, as mentioned above, commercial corticosteroids are practically insoluble in water. This is well known to one of skill in the art. The solubility of corticosteroids, e.g. in pharmaceutically useful oils, is also typically low due to the mismatch between the cholestane backbone of the former and molecular size of the latter. Therefore, corticosteroids tend to form micro-crystals in various formulations unless they are prevented from doing so by use of suitable co-solvents.

Therefore, the use of corticosteroids as active agents in ultradeformable vesicles comprising a mixture of the stable bilayer forming lipid and the bilayer destabilizing amphiphat is not trivial. For practical application, it is necessary to select the largest relative drug amount that, at the same time, does not lead to corticosteroid precipitation and, consequently, to bilayer stiffening and/or clogging of the pores in a semipermeable membrane through which the vesicle should carry the corticosteroid molecules.

Applicant, thus, teaches highly adaptable carrier transporting preparations that transport highly potent corticosteroids reliably and at a high degree through the skin, while avoiding undesirable side effects. Applicants further teach preparations that contain a large amount of corticosteroid (above 0.1 weight-%, relative to total dry mass of the formulation) without causing

adverse effects on the skin and without compromising the stability and deformability properties of the agent carrier.

DE '287, on the other hand, describes transfersomal compositions. It is mentioned that, among the many agents that may be contained within the transformations, corticosteroids can be included. However, DE '287 does not describe or suggest the use of any particular corticosteroids or amounts of corticosteroids in the compositions. Further, DE '287 does not mention or suggest the many problems with respect to the incorporation of corticosteroids into such compositions, e.g. the side effects of corticosteroids, the solubility of the corticosteroids, the influence of the insolubility of the corticosteroids on the stability of the compositions, etc. Further, DE '287 provides no guidance as to how to select a suitable amount of corticosteroid while addressing these issues. This comes purely from the present invention. As set forth above, these problems with relation to corticosteroids are currently an issue and have not yet been adequately addressed. Thus, "modification" or "variation" of the amounts of corticosteroids in the formulations is not a routine matter which a person of ordinary skill in the art could do nor would modification or variation "reasonably lead to the amount of corticosteroid claimed by applicant."

US '685 does not remedy these deficiencies. US '685 describes a W/O skin cream preparation. Such preparations are not at all comparable with transfersomal formulations (for the transport of active agents through the skin) in accordance with the present invention. Regardless, US '685 does not teach or suggest Applicants claimed range of above 0.1 weight-% of corticosteroid relative to the dry mass of the formulation. Rather, US '685 specifically teaches use of a well-known amount of 0.05 weight-% (see examples 4 to 7) and not more. Further, US '685 does not provide any motivation for modifying this amount, much less increasing this amount (much less at least doubling this amount) to reach Applicant's minimal claimed value. Like DE '287, there is no guidance within US '685 as to how to solve the problems with relation to use of corticosteroids in transfersomal formulations.

Thus, Applicant respectfully submits that claim 1 is patentable over DE '287, alone and in combination with US '685. In particular, neither of these cited references describe or suggest a formulation containing corticosteroids present at a relative content of above 0.1 weight-% in accordance with Applicant's teachings. Rather, DE '287 describes formulations which are optimized to provide optimal penetration of barriers. These formulations are described for use with a wide variety of agents, which may include corticosteroids. However, there is no suggested amount of corticosteroid nor is there any guidance as to how one can go about selecting the amount of corticosteroids in view of the many problems with relation to the use of corticosteroids. US ' 685 is equally deficient. US '685 describes W/O cream preparations, which are very different than the types of formulations described by the present invention and DE '287. US '685 mentions the use of agents, which may include corticosteroids. However, the amounts of corticosteroids suggested by US '685 are half the amount (or less than half) of the presently claimed amounts. Further, there is no suggestion or motivation to modify these values so as to come within Applicant's claimed ranges. Rather, one of skill in the art would be motivated, if anything, to decrease the amount of corticosteroids.

Accordingly, reconsideration and withdrawal of the rejections is respectfully requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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